

Appl. No. 09/718,998  
Amdt. dated July 24, 2003  
Preliminary Amendment

PATENT

REMARKS/ARGUMENTS

For the convenience of the Examiner, it is noted that there are now 5 new independent claims (claims 133, 170, 178, 189 and 198). Each of the independent claims is followed by 3 dependent claims, for which claims 134, 135, and 136 are the template. In addition, each of the independent claims has a number of dependent claims that refer to particular positions in the immunoglobulins where amino acids are replaced. Finally, claim 208 is multiply dependent on the 5 independent claims and on 2 dependent claims.

Applicant wishes to point out that the current application is a member of a family of patents and patent applications descending from application No. 07/634,278 filed on Dec. 19, 1990 with priority to No. 07/310,252 filed Feb 13, 1989 and No. 07/290,975 filed Dec. 28, 1988. The newly added claims are related to those in the prior patents, but are in general more specific. For example, claim 133 is related to claim 13 of US 6,180,370 B1, and claim 198 is related to claim 20 of US 5,693,762.

The newly added claims are also related to the other claims now pending in the present case. All of the newly claims are directed to humanized immunoglobulins in which an amino acid from the donor immunoglobulin framework outside the CDRs replaces the corresponding amino acid in the acceptor immunoglobulin framework. Claims 133-177, 179-197 and 199-207 specify designated positions of the amino acid from the donor immunoglobulin substituted into the acceptor framework. Claim 178 specifies the substitution occurs in the humanized immunoglobulin light chain. Claim 198 specifies that the acceptor immunoglobulin heavy chain variable region framework is a consensus sequence.

Support for the amino acid positions listed in claim 133 and in other claims are provided at page 33, line 21 through 30 of the specification and in the experimental examples, e.g., at page 43, line 14 through page 44, line 19; Table 1 on page 54; and at page 196, line 10 through 22. The positions listed in claims 170, 179, 189 and 199 are the exemplified positions for the corresponding category; for example, positions H49, H66, H94 and H103 of claim 170 are listed in Category 3 (see Table 1 on page 54), which is defined on page 32, line 1 through 2 as being adjacent to one of the CDRs. However, the Examiner is informed that two numbering systems

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are in common use to describe the positions of amino acids in immunoglobulin sequences: sequential numbering, and the numbering system of Kabat, which is described on page 127, lines 24 through 30. The numbering system used in the examples is sequential numbering, as is clear, e.g., from the corresponding figures. The numbering system used at p. 33 of the specification is the Kabat system as stated at p. 33, line 28. The Kabat system is preferable because it allows one to determine which amino acids in different antibodies correspond to each other. Hence, for consistency the sequential position numbers in the examples have been replaced by the equivalent Kabat position numbers in the claims. The applicant is prepared to submit an expert declaration, if requested, that this renumbering has been done correctly, i.e., that the Kabat position numbers refer to the same amino acid positions in the examples as the original sequential numbers.

Support for claim 134 may be found, e.g. in Table 1, p. 54 providing five examples of humanized immunoglobulins having 3 CDRs from the heavy chain of a donor immunoglobulin and 3 CDRs from the light chain of a donor immunoglobulin. Support for claims 135 and 136 is found at, e.g., page 5, lines 33 through 35. Support for claim 198 is found at page 29, lines 25 through 28 together with page 30, line 37 through page 31, line 5. Support for claim 208 is found, e.g., at page 39, line 34 through page 40, line 5. Support for claim 209 is found, e.g., at page 72, lines 20 through 30.

Of the references cited on the accompanying IDS, Applicant wants particularly to bring to the Examiner's attention the patents Waldmann et al., US 5,846,534; Carter et al. US 6,407,213 B1; and Winter, US 6,548,640 B1, because these were not cited in the predecessor cases to the current application. However, the '534 patent is equivalent to the European patent application Clark, EP 0328 404 and also describes the same example as Riechmann et al. Nature 332, 323-327, where *were* cited in predecessor cases. The '640 patent, which issued on April 15, 2003, contains the same example as the '534 patent and in addition contains other examples that were previously discussed in another patent, Winter, US 5,225,539 that was also cited in the predecessor cases, as well as in cited scientific publications. The Carter '213 patent, which is directed to certain types of humanized antibodies, has an earliest possible priority date of June

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14, 1991, after the priority date of the present application, and is therefore not prior art against it, but is cited to complete the record.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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